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L3 ANSWER 4 OF 49 CA COPYRIGHT 2003 ACS
AN 136:156403 CA
TI Methods for identifying therapeutic targets for treating infectious disease
IN Shepard, Michael H.; Lackey, David B.; Cathers, Brian E.; Sergeeva, Maria V.
PA Newbiotics, Inc., USA
SO PCT Int. Appl., 503 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002007780	A2	20020131	WO 2001-US23095	20010720

PI W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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PRAI	US 2000-219598P	P	20000720
	US 2000-244953P	P	20001101
	US 2001-276728P	P	20010316

AB This invention provides methods and systems to identify enzymes that act as enzyme-catalyzed therapeutic activators and the enzymes identified by these methods. Also provided by this invention are compds. activated by the enzymes as well as compns. contg. these compds.

L3 ANSWER 36 OF 49 CA COPYRIGHT 2003 ACS
AN 82:53443 CA
TI Effect of sulfhydryl reagents on the activity of histidinolphosphatase from Salmonella typhimurium and bakers' yeast
AU Houston, L. L.; Millay, Robert H., Jr.
CS Dep. Biochem., Univ. Kansas, Lawrence, KS, USA
SO Biochimica et Biophysica Acta (1974), 370(1), 216-26
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB Inhibition of histidinolphosphatase (EC 3.1.3.15) from either a mutant of S. typhimurium or bakers' yeast strongly suggested the involvement of a SH group in the catalytic activity. Inhibition by .mu.M concns. of p-chloromercuribenzoate was noncompetitive with the yeast enzyme, but the mercurial acted as a competitive inhibitor of the Salmonella enzyme. Inhibition was protected against by histidinol. Ethylenimine inhibited yeast phosphatase activity in nearly a 1st order fashion, whereas the reaction with p-chloromercuribenzoate was distinctly biphasic. Other reagents, such as IO4-, iodoacetamide, and N-ethylmaleimide, that react with SH groups also inactivated. The Salmonella enzyme was inhibited by 5,5'-dithiobis(2-nitrobenzoic acid) more rapidly at pH 7 than at pH 8.5; addn. of MnCl2 changed the kinetics of activation at various pH values. The similarity in the involvement of a SH in the inactivation site of the phosphatases indicated that the 2 enzymes may be evolutionary close, even though the Salmonella enzyme is a bifunctional enzyme in wild-type strains having imidazole-glycerolphosphate dehydratase activity in addn. to phosphatase activity.

L3 ANSWER 45 OF 49 CA COPYRIGHT 2003 ACS
AN 77:71752 CA

TI New assay for histidinol phosphate phosphatase using a coupled reaction
AU Brady, D. R.; Houston, L. L.
CS Dep. Biochem., Univ. Kansas, Lawrence, KS, USA
SO Analytical Biochemistry (1972), 48(2), 480-2
CODEN: ANBCA2; ISSN: 0003-2697
DT Journal
LA English
AB The increase in absorbance at 340 m.mu. was detd. for 10 min after the addn. of histidinol phosphate phosphatase (I) to the assay mixt. contg. 0.1M triethanolamine-HCl buffer, pH 7.5, 0.01M MnCl2, 0.1M histidinol phosphate (II), 0.3M NAD, and 50 .times. 10-4 units histidinol dehydrogenase (III) from Salmonella typhimurium His 01242. Increasing the conc. of III did not increase the rate of NADH formation. Results with this assay were comparable to those using the molybdate-ascorbate assay. The coupled assay was linear up to 0.13 absorbance unit/min; it was satisfactory for crude exts. in the presence of large amts. of protein. Sometimes a baseline correction without II was needed due to NAD reducing enzyme in crude material. The correction amounted to <0.04%/min of the total NAD.

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L1 ANSWER 7 OF 7 REGISTRY COPYRIGHT 2003 ACS
RN 9025-79-0 REGISTRY
CN Phosphatase, histidinol- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN E.C. 3.1.3.15
CN Histidinol phosphatase
CN **Histidinol phosphate phosphatase**
CN **L-Histidinol phosphate phosphatase**
MF Unspecified
CI MAN
LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, EMBASE, TOXCENTER

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60/276,728	16 March 2001 (16.03.2001)	US

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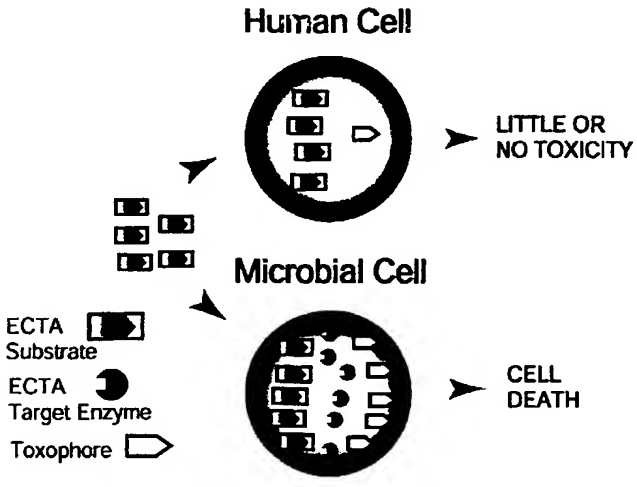
(54) Title: METHODS FOR IDENTIFYING THERAPEUTIC TARGETS FOR TREATING INFECTIOUS DISEASE



ECTA technology utilizes preferentially expressed enzymes in pathogenic organisms to generate cytotoxins.

(57) Abstract: This invention provides methods and systems to identify enzymes that act as enzyme catalyzed therapeutic activators and the enzymes identified by these methods. Also provided by this invention are compounds activated by the enzymes as well as compositions containing these compounds.

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METHODS FOR IDENTIFYING THERAPEUTIC TARGETS FOR TREATING INFECTIOUS DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional patent applications having the serial numbers 60/219,598; 60/244,953; and 60/276,728, filed July 20, 2000; November 1, 2000; and March 16, 2001, respectively. The contents of these applications are hereby incorporated by reference into the present disclosure.

TECHNICAL FIELD

The present invention relates to the field of Enzyme Catalyzed Therapeutic Activation (ECTA™) therapy and in particular, ECTA therapies targeting intrinsic and unique enzymes in pathogenic microorganisms or in host cells.

BACKGROUND OF THE INVENTION

Throughout and within this disclosure, various publications, patents, published patent applications and references are identified by first author and date, within parentheses, patent number, publication number or by web address. If the complete bibliographic citation is not provided after the publication or reference, it is at the end of the specification, immediately preceding the claims. The disclosures of all publications, references and information provided at the web addresses are hereby incorporated by reference into this disclosure to more fully describe the state of the art to which this invention pertains.

The resistance of bacterial, fungal, and viral pathogens to drug therapy has become a health issue of global concern. Similarly, the resistance of cancer cells to chemotherapy is responsible for about 600,000 deaths each year in the United States. While there are important differences that distinguish these different diseases, there are also important unifying concepts. For this reason, the introduction to this patent application will

focus on bacterial drug resistance mechanisms, and refer to common issues with other diseases as appropriate.

When antibiotics became widely available in the middle of the twentieth century (approximately 50 years ago), they were hailed as miracle drugs--magic bullets able to eliminate bacterial infection without harm to the normal cells of treated individuals. Yet with each passing decade, drug-resistant bacteria and other drug-resistant pathogens have emerged with increasing frequency. Simple bacterial and fungal infections that were once eliminated with a single drug and a simple course of therapy have become life threatening, and can be successfully treated only with drugs that display significant toxicity. Similarly, the tremendous optimism that followed initial clinical use of protease and reverse transcriptase inhibitors in the treatment of human immunodeficiency disease has now been replaced with complex cocktails of agents, and the understanding that resistant strains of virus will develop (Armstrong and Cohen (1999)).

An important reason why resistance has continued to develop at such a rapid rate, in all fields of infectious disease, is that the discovery and development of antibiotics has focused on only a few targets and a few mechanisms. By far the most common approach to discovery of anti-infectives has been the search for inhibitors of bacterial, fungal or viral enzyme functions. Antibiotics to treat the most common bacterial infections attack only a few distinct targets in the pathogen (Neu (1992)). For example, beta-lactams, penicillins, cephalosporins, monobactams, carbapenems, and penems are Class I inhibitors of bacterial cell wall synthesis. The glycopeptides vancomycin and teicoplanin are examples of Class II inhibitors of cell wall synthesis. Clindamycin, chloramphenicol, tetracyclines, and aminoglycosides are examples of known inhibitors of protein synthesis. Ciprofloxacin and ofloxacin are known inhibitors of DNA gyrase.

Each of these drugs targets an important enzyme. For difficult infections, combinations of these and other drugs are often utilized. However, the combination of drugs often works toward inhibition of separate

enzyme targets. For instance, in bacterial and sometimes fungal infections, the combination of trimethoprim and sulfomethoxazole is used to simultaneously inhibit dihydrofolate reductase and dihydroopterate synthetase, respectively. Similar approaches are used for the treatment of viral infections and cancer. In anti-HIV therapy the combination of reverse transcriptase and viral protease inhibitors is commonly employed. In treatment of breast cancer, cocktails that include a fluoropyrimidine and methotrexate, inhibitors of thymidylate synthase and dihydrofolate reductase, respectively, are often used.

It can therefore be seen that inhibitors of enzyme function are favored for the development of drug treatments in cancer and infectious disease. However, this approach has led to the emergence of drug resistant strains that render the original therapeutic ineffective. Antimicrobial agents are rendered inactive by four major mechanisms (Reviewed in Schmitz and Fluit (1999)):

(I). Enzyme mediated. This is the most common inactivation scheme observed in laboratory and clinical bacterial strains. For example, beta-lactam antibiotics work by inhibiting cell wall synthesis, specifically they inhibit penicillin binding protein. In some cases though, bacteria express a beta-lactamase enzyme which hydrolyses the antibiotics so they become inactive. Bacteria that express a beta-lactamase are often beta-lactam-antibiotic resistant. Pathogens can also enzymatically modify a therapeutic so that it cannot bind to its target (as seen with aminoglycosides and chloramphenicol). In both of the cases outlined above, an enzyme encoded by the pathogen mediates resistance.

(II). Membrane permeability. Pathogens adapt and change their cell wall (the porin structures) to prevent drug entry. This can occur in response to almost any antibacterial agent.

(III). Drug efflux pumps. Pathogens adapt and change membrane transport proteins (also an enzyme family), such that they operate with increased efficiency toward the antibiotic. This is an important mechanism of resistance to tetracycline.

(IV). Target mutation. Pathogens mutate the therapeutic target thereby preventing activation of the antibiotic. Common mutations occur in the penicillin binding protein, which prevents activation of the antibiotic.

In the hospital setting, the most recent worrisome resistance traits to emerge include plasmid-mediated resistance to imipenem and to third-generation cephalosporins among nosocomial gram-negative bacteria, and the acquisition of resistance to vancomycin by enterococci. Methicillin-resistant staphylococci continue to be a problem, with about 75% of clinical strains found to be resistant to the penicillin-related drugs, and increasingly resistant to numerous other agents. The most important resistance traits seen in community-acquired organisms include beta-lactam resistance in *Streptococcus pneumoniae* and combined ampicillin and chloramphenicol resistance in *Haemophilus influenzae*. Shigellae resistant to essentially all commonly used oral agents are also a problem, particularly in developing countries (Reviewed by Murray, B. (1997)).

While there are important differences in the exact mechanisms of drug resistance between bacterial, fungal and viral pathogens, a common theme is present throughout. Most commonly, enzyme inhibitors are selected for drug development and use in the clinic. Similarly, inhibitors of enzyme function are commonly used in the treatment of cancer (McVie (1999)). In each of these cases, drug resistance is characterized by increased enzyme expression, mutation of the target enzyme (so that it no longer recognizes the inhibitor), changes in target cell permeability and the development or overexpression of efflux pumps. There is no end is in sight to the problem of drug resistance and, thus, new strategies to prevent and control resistant pathogens and tumor cells continue to be necessary.

Thus, a need exists for a novel approach to the development of anti-infective agents that overcome the drawbacks of current inhibitor-based therapeutic approaches. Various aspects of this invention satisfy this need by providing methods and systems to identify target enzymes and methods to design and assay novel therapeutic prodrugs activated by these enzymes.

DISCLOSURE OF THE INVENTION

This invention provides a vertically integrated drug discovery program that Applicant has utilized to identify therapeutic enzyme targets and which can be used to identify prodrugs which act by a unique mechanism of action (termed "Enzyme Catalyzed Therapuetic Activation" or "ECTA"™). In one aspect, the invention provides systems and methods to identify enzyme targets *in silico*. In alternative aspect, the invention provides a method to design potential prodrugs activated by the enzyme targets. In a yet further aspect of this invention, *in vitro* and *in vivo* assays are provided. The assays and prodrugs also are useful to test potential therapeutics. Further provided are methods to inhibit the growth of target organisms, cells, or host cells using the prodrugs of this invention. Methods to treat or alleviate the symptoms of selected diseases are further provided using the prodrugs of this invention.

In one aspect, the *in silico* methods comprise selecting from a suitable database an enzyme or list of enzymes expressed by a target organism, by an infectious agent or in an infected host cell, or by or in a pathological cell. The results of this search are compared against a search of expressed enzymes in or by a suitable control The method selects for enzymes expressed in one cell type or organism but not in another. Various embodiments of this aspect are provided herein. For example, one embodiment identifies enzymes expressed by a pathogen or on in a pathogen-infected cell but not expressed in the host or uninfected host cell.

These methods identified and will identify enzymes that are targets ("target enzymes") for a novel ECTA approach to treat a variety of diseases including bacterial, fungal, parasitic and viral infections. In contrast, conventional therapies rely on the use of inhibitors of enzymes critical for target viability and/or proliferation. Consistent with Applicant's ECTA approach, the prodrug compounds of this invention do not act as enzyme inhibitors but undergo enzyme catalyzed transformation by target enzymes

resulting in the generation of cytotoxic reaction product(s). The formation of cytotoxic species is achieved by engineering unique substrates (ECTA prodrugs or compounds) which are transformed into toxins by the target enzymes.

In one aspect, the target enzymes of this invention are pathogen-specific enzymes that are only expressed by pathogens, e.g., bacterial and fungal pathogens or in virally infected cells. In cases of intracellular parasites or viruses, host cell enzymes induced by the pathogen or infectious agent, or enzymes specifically encoded by the pathogen or infectious agent, were targeted and can be targeted in further embodiments of this invention.

The pharmaceutical and agricultural industries have focused on development of inhibitors of selected target enzymes for the development of anti-infectives, insecticides and herbicides (Shaner and Singh (1997) and Papamichael (1999)). This approach has suffered from several issues: (1) the presence of salvage pathways which allow specific enzyme inhibition to be circumvented; (2) mutation of the enzyme so that it no longer binds inhibitor, but can still metabolize substrate; and (3) inhibitor-associated enzyme overexpression leading to resistance.

The use of enzyme inhibitors for treatment can often result in harmful and uncomfortable side effects. For example, protease inhibitors used in HIV treatment have been shown to affect glucose control, lipid metabolism, and body fat distribution (Mulligan (2000)).

This invention defines a new ECTA approach that targets intrinsic enzymes ("iECTA" approach) which overcomes the limitations and problems associated with prior art therapies. Applicant's approach is distinguished from prior approaches because iECTA enzymes are NOT endogenous enzymes for the host cell and are not necessarily related to drug resistance. In other words, only pathogens or pathogen-infected cells express the iECTA enzymes. The prodrug compounds which are designed to be selectively activated by the iECTA enzymes also avoid side effects by achieving alternative, more selective therapies that preferentially affect diseased cells

with little or no effect on healthy tissue. To the best of Applicant's knowledge, this approach has not been described or utilized previously. Therapeutics designed and generated using iECTA technology supplement and complement present day enzyme inhibitor-based treatments.

The present method can be applied to identify target enzymes other than iECTA enzymes by searching a first suitable data structure (database) to obtain a first set of information relating to one or more enzymes associated with a target organism. In certain embodiments, the enzyme is overexpressed or selectively expressed as compared to a control counterpart. A search also is conducted on one or more other suitable data structures (databases) to obtain one or more additional sets of information relating to one or more expressed enzymes associated with one or more additional class of organisms or by the same organism growing under in a different environment or in a different host. The first set of information is compared to the one or more additional sets of information to identify enzymes in the first set of information that are not present in the one or more additional sets of information. These identified enzymes are targets for ECTA compounds.

This invention further provides ECTA prodrugs. While each prodrug is selectively activated by a specific target enzyme counterpart, there are some general features of ECTA prodrugs. Figures 2A and 2B describe general characteristics of ECTA prodrugs that distinguish them from conventional therapeutics. One feature of an ECTA enzyme/ECTA compound combination is the absence of irreversible inhibition or inactivation of the target enzyme by the ECTA compound, intermediates or products of the reaction. In some embodiments, it is preferred but not necessary, that the ECTA target enzyme be critical for disease progression. This property means that resistance to iECTA compounds, which could result from disease/loss of target enzyme expression, may also result in decreased pathogenicity. To the best of Applicant's knowledge, this approach has not been previously described or utilized.

Also provided is a method for the design of iECTA compounds or prodrugs which are selectively activated by yet to be identified iECTA enzymes using the methods of this invention. This invention further provides iECTA compounds or prodrugs activated by infectious agents or in host cells, e.g., the enzymes listed in Figure 7A and 7B and their biological equivalents. As used herein, and unless specifically excluded, Applicants intend for the biological equivalents of the iECTA compounds to be included in each embodiment of the invention. A "biological equivalent" is defined *infra*.

The iECTA compounds are provided alone or in combination with a liquid or solid carrier. Compositions comprising at least one iECTA compound or its biological equivalent in combination with an additional therapeutic is further provided by this invention.

Also provided is an assay for an iECTA compound that selectively inhibits the growth of an infectious agent in a target cell or an infected cell. The iECTA prodrug is contacted with its target enzyme in a cell-free system under suitable conditions. Activation by the target enzyme is monitored by methods well known in the art.

An *in vitro* screen is further provided by this invention. The iECTA enzyme is contacted with a pathogen or host cell containing or expressing the target enzyme. In one embodiment, the host cell and the prodrug are contacted under conditions that that favor incorporation of the compound into the host cell. The pathogens or host cells are assayed for inhibition of growth or killing of the infectious agent or the host cell. Control systems and/or cells can be contacted with the prodrug and assayed.

This invention also provides a method for inhibiting the growth or proliferation of an infectious agent or a host cell by contacting the infectious agent or host cell with an effective amount of an ECTA prodrug, e.g., an iECTA prodrug.

A method for determining whether a subject will be suitably treated by an ECTA prodrug such as an iECTA prodrug is provided by this invention. As an example, an iECTA compound is delivered to an infected cell under

suitable conditions such that the growth of the infectious agent or infected cell is inhibited or the agent is killed.

Various modifications of the above methods are within the scope of this invention. For example, a different and/or additional enzyme target can be assayed against the same iECTA prodrug or a different and/or additional prodrug can be assayed against the same target enzyme. Prior art therapeutics or therapeutic methods can be combined with the use of the iECTA prodrugs to enhance or modify the biological activity of the iECTA prodrug. These methods can also be modified by varying the amount of the iECTA prodrug and/or additional therapeutic or alternatively or in combination, the order of the prodrugs and/or therapies can be modified, e.g., simultaneous or sequential. The sequential order can further be modified. These methods are further modified for prophylactic use.

A kit for determining whether a pathogen or pathogen-infected cell will be suitably treated by an iECTA therapy is also provided by this invention. The kit comprises an effective amount of at least one compound of this invention and instructions for use.

As is apparent to those of skill in the art, the above iECTA methods can be modified for application in other ECTA systems. These systems are described in more detail below.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows how ECTA technology preferentially targets selected cells.

Figures 2A and 2B are the process for successful identification of one embodiment of this invention, the identification of iECTA target enzymes and iECTA compounds.

Figure 2C is a flowchart for a process for identifying enzymes for designing ECTA compounds in accordance with an embodiment of the present invention.

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               S 9025-79-0/REG#

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L6             1 S HISTIDINOLPHOSPHATASE
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L10            0 S USPATFUL

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L16            6 S L15 OR L13

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